Hormone Receptor Status as a Prognostic Factor in Breast Cancer Patients With Hepatic Metastases Treated by Liver Resection

To the Editor:

We read with great interest the article by Adam et al[1] regarding liver resection for patients with hepatic metastases from breast cancer. Authors found that failure to respond to preoperative chemotherapy, a R2 resection, and the absence of repeat hepatectomy were independently associated with poorer survival. However, they did not mention hormone receptor status of the patients, which might have an effect on the survival rate. In their analysis, estrogen (ER) positive and progesterone (PR) positive patients had a longer survival than ER negative and PR negative patients (median survival, 50 and 87 months for ER and PR positive patients, respectively, and 27 and 29 months for ER and PR negative patients, respectively). Although these results were not implicating hormone receptor status as an independent variable, there is a trend for hormone receptor patients to have a longer survival. Moreover, Elias et al[2] in their study evaluated 54 breast cancer patients with liver metastases as the sole site of metastatic disease (except for bone metastases in 3 patients) who underwent hepatectomy. They showed that the only factor influencing survival in both the univariate and multivariate analyses was the hormone receptor status ($P = 0.03$), and the relative risk of death was found to be increased by 3.5-fold when hormone receptor was negative. Given the information above, hormone receptor status of breast cancer patients with hepatic metastases may also be considered for the selection of patients who are candidates for liver resection.

Tugrul Purnak, MD
Department of Internal Medicine
Hacettepe University Faculty of Medicine
Ankara, Turkey

Kadri Altundag, MD
Department of Medical Oncology
Hacettepe University Faculty of Medicine
Ankara, Turkey
altundag66@yahoo.com

REFERENCES

1. Adam R, Aloia T, Krissat J, et al. Is liver resection justified for patients with hepatic metastases from breast cancer? *Ann Surg*. 2006; 244:897–908.
2. Elias D, Maisonnette F, Druet-Cabanac M, et al. An attempt to clarify indications for hepatectomy for liver metastases from breast cancer. *Am J Surg*. 2003;185:158–164.

Reply:

We appreciate Dr. Purnak's and Dr. Altundag's comments regarding our recent publication in the *Annals of Surgery*. The authors correctly note that hormone receptor status is an important prognostic indicator in patients with localized breast cancer, that our statistical analysis showed a trend toward a survival advantage in receptor positive patients undergoing resection of hepatic metastases, and that Elias et al found a strong association between hormone receptor status and survival after hepatic resection of breast cancer liver metastases. The statistical strength differences for this variable between our study and Dr. Elias' study may be due to differences in the number of patients analyzed (54 vs. 85 patients) and differences in patient selection/characteristics.

On the basis of our analysis, however, we would disagree that patient selection for hepatic resection of breast cancer liver metastases should be based solely on the hormone receptor status. Although this factor should be used to counsel patients regarding the postoperative prognosis and need for postoperative systemic therapy and close surveillance, if a breast cancer patient has resectable intrahepatic disease, controlled extrahepatic disease, and a favorable response to preoperative systemic therapy, we would strongly advocate for surgical therapy regardless of hormone receptor status.

In summary, we would agree to consider hormonal receptor status as a favorable prognostic factor when positive but not as a contraindication to liver surgery when negative.

René Adam, MD, PhD
Thomas Aloia, MD
Paul Brousse Hospital
Villejuif, France
rene.adam@pbr.ap-hop-paris.fr

Impact of Laparoscopic Resection for Colorectal Cancer on Operative Outcomes and Survival

To the Editor:

I would like to congratulate Dr. Law and colleagues for their recent study reporting their experience with laparoscopic colectomies.[1] This study is just one of their many fine contributions to the field of colorectal surgery. Two main conclusions can be drawn from their study, ie, laparoscopic colectomy results in shorter postoperative convalescence and more controversially, laparoscopy is associated with improved short-term survival compared with open surgery.

The findings of Law et al that laparoscopically treated patients who have significantly earlier return of bowel function, earlier resumption of diet, and shorter hospitalization are supported by several randomized controlled trials (RCTs)[2–4] and hence seem irrefutable. However, one must still remain cautious when interpreting these results because it is important to note that none of these studies were double-blinded. Hence, biases resulting from patient and surgeon attitudes and practices remain. The influence of laparoscopic surgery on improved outcomes in unblinded patients may be akin to the "placebo" effect, whereby patients are more motivated after what they perceive as having undergone a more minor "key hole" surgery. Unblinded surgeons may also contribute to the improved postoperative outcomes because surgeons may adopt more aggressive attitudes towards early feeding and discharge after laparoscopy. This bias is evident in Table 3 of the study,[1] whereby it can be observed that although the minimum time to pass first flatus or first bowel motion was 0 days in the open group, the minimum time to first fluid or solid intake was 1 and 2 days, respectively. Con-

versely in the laparoscopic group, although the minimum time to pass first flatus or first bowel motion was 1 day, the minimum time to first fluid or solid intake was 0 days. The authors also observed that there was a trend towards a shorter postoperative convalescence over the 2 time periods in patients undergoing open surgery, which provides indirect evidence that the managing surgeons' attitudes and practices can have an important influence on postoperative outcome.

The second conclusion drawn by the authors was that laparoscopy was associated with an improved 3-year overall survival compared with open surgery. This result, although compatible with the results from the RCT by Lacy et al,[4] is not supported by the other RCTs,[2,3] and the explanation for this is unclear. Although the authors suggested that favorable immunologic factors may explain the difference, several other reasons may account for their observations. First, selection bias is likely to be a major source of bias in their nonrandomized study. Although not statistically significant, it can be observed that patients in the laparoscopic group had smaller tumors, lower stage, and lower American Association of Anaesthetists (ASA) score status, compared with patients in the open group. These factors as a whole are likely to contribute to the improved short-term survival in the laparoscopic group. Furthermore, the higher postoperative mortality observed in the open group is another potential contributing factor to the decreased 3-year survivals observed in the open group. Were operative deaths censored or included as events in their calculation of actuarial survivals?

Finally, the duration of follow-up of patients is an important factor when predicting survivals via the Kaplan–Meier method. The observed improved survival in the laparoscopic group could be secondary to the shorter follow-up in this group compared with that in the open group. Although the analysis was confined to the period between June 2000 and December 2004, it is possible that most of the laparoscopic cases were performed in the latter part of the study compared with the open group, and hence had a shorter follow-up. Thus, it is important for us to know the mean and median follow-up times of the laparoscopic versus the open group, which was not reported in the study. From my observation of the survival curves in the study (Figs. 1–4),[1] it would certainly seem that patients in the laparoscopic group had shorter follow-up. For example in Figure 4, the latest time for an "event" (death in this case) to occur in the survival curve was 36 months in the laparoscopic group and no "event" occurred after this. Contrastingly in the open group, multiple "events" occurred between 36 and 48 months suggesting that patients in this group had longer follow-up.

Brian K. P. Goh, MBBS, MRCS, MMed
Department of Surgery
Singapore General Hospital
Singapore
bsgkp@hotmail.com

REFERENCES

1. Law WL, Lee YM, Choi HK, Seto CL, Ho JW. Impact of laparoscopic resection for colorectal cancer on operative outcomes and survival. *Ann Surg*. 2007;245:1–7.
2. Nelson H, Sargent DJ, COST Study Group. A comparison laparoscopic assisted and open colectomy for colon cancer. *N Engl J Med*. 2004; 350:2050–2059.
3. Guilloi PJ, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopically-assisted surgery in patients with colorectal cancer (MRC CLASSICC trial): multicentre, randomised controlled trial. *Lancet*. 2005;365:1718–1726.
4. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet*. 2002; 359:2224–2229.

Reply:

We appreciate Dr. Goh's interest in our article[1] and his concern regarding our interpretation of the results was well considered. We reported the results and the impact of adopting laparoscopic colectomy in patients with colorectal malignancy in a high volume center over a 9-year period. We found that laparoscopic resection was associated with better short-term outcomes in terms of shorter duration of ileus, earlier resumption of feeding, and shorter hospital stay. Admittedly, the study was not a randomized trial and standardized perioperative care was not implemented during the study period. Biases in the postoperative management were unavoidable. However, in the second period of the study, the postoperative management, both in the open and laparoscopic groups, aimed at early feeding and early mobilization. The resumption of diet was based on the clinical judgment of the surgeons and was not delayed until the passage of flatus or bowel movement. The minimum time to start diet for patients in the open group on day 1 would just demonstrate that the general wellbeing of the patients did not allow them to tolerate oral diet intake in day 0. The demonstration of improvement in short-term outcomes was actually compatible with the results of most of the published randomized controlled trials,[2,3] in which the perioperative management was also based on the surgeons' judgment and was not in the form of a standardized recovery program. Recent studies showed improved short-term outcome with the application of enhanced recovery program in both open and laparoscopic colectomy.[4–6] Published results from randomized studies, which compared laparoscopic with open with standardized postoperative, were not conclusive. Basse et al did not show any difference between laparoscopic and open resection in patients with the enhanced recovery program,[7] whereas King et al showed improved short-term outcome in patients who underwent laparoscopic surgery.[8] However, in both studies, the number of patients was small. Large-scale randomized trials to compare the surgical approaches with a standardized postoperative program are certainly necessary to avoid the bias of the surgeons in the postoperative management.

Concerning Dr. Goh's comments on our results on survival, we would like to clarify that in the analysis of survival, patients who died in the postoperative period (30 days) were excluded. The stage, size, and the ASA status were not statistically significant when the 2 groups were compared. In the analysis of survival, we also stratified according to the stage and the results were shown in Figures 2–4 in the article. The better survival in stage III patients (although not statistically significant) was compatible with Lacy et al's results.[3] Actually, better survival in patients with node pos-

itive disease was also shown in the study by Capussotti et al.[9] Concerning the median follow-up of the 2 groups of patients, in contrary to what Dr. Goh thought, the median follow-up period for the laparoscopic group is actually longer than that for open surgery. We compared the 2 groups of patients with Kaplan–Meier method and log-rank test, which is the recommended method for comparison of survival in patients with different duration of follow-up.

Wai Lun LAW, MS, FRCS (Edin.), FACS
Department of Surgery
University of Hong Kong Medical Centre
Queen Mary Hospital
Hong Kong
lawwl@hkucc.hku.hk

REFERENCES

1. Law WL, Lee YM, Choi HK, et al. Impact of laparoscopic resection for colorectal cancer on operative outcomes and survival. *Ann Surg*. 2007;245:1–7.
2. The Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med*. 2004;350:2050–2059.
3. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet*. 2002; 359:2224–2229.
4. Basse L, Hjort JD, Billesbolle P, et al. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg*. 2000;232:51–57.
5. Delaney CP, Zutshi M, Senagore AJ, et al. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum*. 2003;46: 851–859.
6. Raue W, Haase O, Junghans T, et al. 'Fast-track' multimodal rehabilitation program improves outcome after laparoscopic sigmoidectomy: a controlled prospective evaluation. *Surg Endosc*. 2004;18:1463–1468.
7. Basse L, Jakobsen DH, Bardram L, et al. Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. *Ann Surg*. 2005;241:416–423.
8. King PM, Blazeby JM, Ewings P, et al. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Br J Surg*. 2006;93:300–308.
9. Capussotti L, Massucco P, Muratore A, et al. Laparoscopy as a prognostic factor in curative resection for node positive colorectal cancer: results for a single-institution nonrandomized prospective trial. *Surg Endosc*. 2004;18:1130–1135.

Steatosis as a Risk Factor in Liver Surgery

To the Editor:

We read with interest the article by Veteläinen et al entitled "Steatosis as a Risk Factor in Liver Surgery" in the January 2007 issue of *Annals of Surgery*.[1] We agree with the authors that the full impact of hepatic steatosis on outcomes after liver surgery is only beginning to be understood. However, recent data have clearly delineated a subset of patients in whom steatosis may be most relevant—those with steatohepatitis, who are at increased risk for liver failure and death after major liver resection.

Slow progress in understanding the impact of steatosis on outcomes after major liver surgery may be related in part to a failure to distinguish between steatohepatitis and uncomplicated steatosis (without significant inflammation and other changes). Although it is increasingly clear that uncomplicated steatosis may be associated with more bleeding during parenchymal transection[2] and more posthepatectomy complications, including infections,[3] steatosis has not been associated with a significant increase in mortality.[4] In contrast, however, several authors have recently shown that patients with steatohepatitis may be at higher risk for liver failure and death after major hepatectomy.[5,6]

A clear understanding of the difference between steatosis and steatohepatitis was recently provided in a simple, objective pathologic grading system for steatohepatitis proposed by Kleiner et al for the Nonalcoholic Steatohepatitis Clinical Research Network.[7] The "Kleiner score" provides a reproducible means of evaluating liver specimens for nonalcoholic fatty liver disease and is based on 3 simple, objective factors scored on standard hematoxylin and eosin-stained liver parenchyma: percentage parenchymal involvement by steatosis, degree of lobular inflammation, and degree of ballooning of hepatocytes.

An important element of this scoring system is that disease can be classified as severe steatohepatitis even if there is only a minor degree of steatosis. Furthermore, the score is clinically relevant. We recently analyzed outcome after hepatectomy for colorectal liver metastases in 406 patients whose resected liver parenchyma was subjected to systematic pathologic analysis.[6] We demonstrated that patients with steatohepatitis (Kleiner score ≥ 4) had a significantly higher 90-day posthepatectomy mortality rate than did patients who did not have steatohepatitis (14.7% vs. 1.6%; odds ratio 10.5; $P = 0.001$). Whether the risk associated with steatohepatitis relates to failure of the steatohepatitic liver to regenerate after hepatectomy is unclear, but Veteläinen et al's observation that adenosine triphosphate (ATP) storage is impaired in patients with obesity-related steatohepatitis may provide a basis for this hypothesis.

Among the spectrum of drug-induced hepatic injuries, steatohepatitis is a distinct subtype. The study from our group also analyzed the pathologic changes in the nontumorous liver associated with specific chemotherapy regimens.[6] No specific chemotherapy regimen was associated with steatosis when steatohepatitis was excluded. However, treatment with irinotecan was associated with the development of steatohepatitis whereas treatment with other agents (5-fluorouracil alone or oxaliplatin) was not. Furthermore, oxaliplatin was associated with sinusoidal injury, not steatosis or steatohepatitis, and resection in patients with sinusoidal injury was not associated with an increase in mortality—a finding subsequently confirmed by others.[8]

Uncomplicated steatosis is a common finding in resected liver parenchyma but appears not to be associated with a major risk of death after hepatectomy. In contrast, steatohepatitis is associated with an increased risk of liver failure and death after hepatectomy. Further understanding of the influence of various histopathologic liver changes on outcome after hepatectomy will require careful evaluation of the liver using standardized pathologic assessment. Collective reference to liver injuries as "steatosis" or "chemotherapy related" must be viewed as an oversimplification of a complex spectrum of injuries that includes simple steatosis, steatohepatitis, sinusoidal injury, and combinations of these and other injuries, particularly

in light of data indicating agent-specific injuries that portend different outcomes.

Eddie K. Abdalla, MD
Jean-Nicolas Vauthey, MD
Department of Surgical Oncology
The University of Texas M. D. Anderson Cancer Center
Houston, Texas
eabdalla@mdanderson.org

REFERENCES

1. Veteläinen R, van Vliet A, Gouma DJ, van Gulik TM. Steatosis as a risk factor in liver surgery. *Ann Surg*. 2007;245:20–30.
2. Behrns KE, Tsiotos GG, DeSouza NF, et al. Hepatic steatosis as a potential risk factor for major hepatic resection. *J Gastrointest Surg*. 1998;2:292–298.
3. Belghiti J, Hiramatsu K, Benoist S, et al. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg*. 2000;191: 38–46.
4. Kooby DA, Fong Y, Suriawinata A, et al. Impact of steatosis on perioperative outcome following hepatic resection. *J Gastrointest Surg*. 2003;7: 1034–1044.
5. Fernandez FG, Ritter J, Goodwin JW, et al. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. *J Am Coll Surg*. 2005;200:845–853.
6. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol*. 2006;24:2065–2072.
7. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*. 2005;41:1313–1321.
8. Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. *J Clin Oncol*. 2006;24:4983–4990.

Reply:

We thank Dr. Abdalla and Dr. Vauthey for their interesting comments. The spectrum of liver injury associated with nonalcoholic fatty livers is indeed complex and requires more detailed discussion. The "Kleiner score" is an important step forward in classifying steatohepatitis, which is unequivocally associated with an increased risk of posthepatectomy liver failure. Although steatotis per se has not been identified as a major risk factor for mortality after liver resection, it was an independent predictor of postoperative complications in several studies.[1] Also, in a model of mild steatosis in the rat, we showed increased hepatocellular damage and impaired functional recovery after 70% liver resection.[2] These findings suggest that steatosis, even in the absence of inflammatory and fibrotic changes, potentially gives rise to parenchymal injury in the regenerating liver, which is likely due to mitochondrial dysfunction. We still believe, therefore, that caution is justified when assessing patients with uncomplicated steatosis for major liver resection. Our understanding of the risks of liver steatosis is rapidly evolving, and we appreciate the important contributions of Dr. Abdalla and Dr. Vauthey in this field.

Thomas M. van Gulik, MD
Reeta Vetelaïnen, MD
Academic Medical Center
Amsterdam, The Netherlands
t.m.vangulik@amc.uva.nl

REFERENCES

1. McCormack L, Petrowsky H, Jochum W, et al. Hepatic steatosis is a risk factor for postoperative complications after major hepatectomy: a matched case-control study. *Ann Surg*. 2007; 245(6):923–930.
2. Vetelainen R, Bennink RJ, van Vliet AK, et al. Mild steatosis impairs functional recovery after liver resection in an experimental model. *Br J Surg*. 2007 May 11; [Epub ahead of print].